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EXAMINER
LOEB, BRONWEN

ART UNIT	PAPER NUMBER
1636	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/848,095	Applicant(s) SHORT ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This action is in response to the communication regarding the sequence dated 18 January 2002.

Claims 1-53 are pending.

Sequence Compliance

1. The specification has been amended to recite SEQ ID Nos. 1 and 2 on p. 66 in accordance with p. 69 in parent 08/876,276. This informal amendment places the application in sequence compliance.

Specification

2. The disclosure is objected to because of the following informalities: In the Abstract, the word "nucleic" is misspelled on line 3.

On p. 41 [0147] a "β" appears to be missing in four instances.

On p. 42 [0148] a "β" appears to be missing in three instances.

On p. 54 [0185] there is a reference to "Figure X" however there is no such figure provided. Also, there appears to be a typographical error in the phrase "which can the be decorated"; should it be "then"?

On p. 56 [0189] in the phrase "liquid grown culture", should it actually be "growth"?

On p. 57 [0197] line 2 the phrase "compounds can are utilized" is grammatically incorrect.

Appropriate correction is required.

Drawings

3. The drawings are objected to because in Figure 7, "fluor" is misspelled; Figure 14 states "from host" whereas in the Brief Description of the Drawings, it appears that the correct phrase should be "the library"; and in Figure 15 "growth" is misspelled. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claims 2, 10, 13, 15, 20, 27, 28, 36, 39, 41 and 46 are objected to because of the following informalities:

Claims 2 and 28 lack the word "which" in the phrase "provided by an enzyme which is selected from".

In claims 10 and 36, the word "extremophiles" is misspelled. In claims 13 and 39, there is a duplication of the word "the".

In claims 15 and 41, it appears the preposition in the phrase "occurs at about 30 minutes" should be "for".

In claims 20 and 46, there appears to be a word or phrase missing, such as "library in".

In claim 27, the word "encapsulation" should be "encapsulating" to indicate the active method step.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-53 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because step b) recites that a bioactivity or biomolecule is detected by a difference in the substrate whereas step c) recites that an analyzer or assay detects the bioactivity of biomolecule. Also, step b) recites "a difference in the substrate" whereas step d) recites "a change in the substrate" is indicative of a DNA that encodes a bioactivity or biomolecule. In both instances, the claim lacks internal consistency which renders the metes and bounds uncertain.

Claim 1 is vague and indefinite because it lacks a method step that clearly relates back to the preamble. The preamble states identifying bioactivities or biomolecules. The recited method steps merely identify clones which have a DNA encoding a bioactivity or biomolecule.

Claim 1 recites the limitation "the DNA" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 recites the limitation "the Streptomyces" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the expression library" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "the samples" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 recites the limitation "the prokaryotic cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 is vague and indefinite it lacks a method step that clearly relates back to the preamble. The preamble states identifying bioactivities or biomolecules. The recited method steps merely identify clones which have a DNA encoding a bioactivity or biomolecule.

Claim 31 recites the limitation "the Streptomyces" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 34 recites the limitation "the expression library" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 39 recites the limitation "the samples" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Double Patenting

7. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to

identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8. Claims 16, 17, 42 and 43 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 11 and 42 of prior U.S. Patent No. 6,174,673. This is a double patenting rejection.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-15, 18-41 and 44-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,174,673. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims are generic to the patented claims. For instance, “bioactive substrate” as recited in the pending claims is generic to “bioactive fluorescent substrate” in the allowed claims. Similarly, “analyzer” is generic to “fluorescent analyzer”. A species renders obvious a genus therefore the

pending claims are rendered obvious by the patented narrower claims in U.S. Patent No. 6, 174,673.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

12. The following art rejections are directed only to those embodiments claimed in the pending application that have not been patented in USP 6,174,673 (in which the embodiment comprising a bioactive fluorescent substrate and a fluorescent analyzer was patented).

13. Claims 1-4, 6-10, 18, 19, 23-30, 32-36, 39-41, 44, 45 and 51-53 are rejected under 35 U.S.C. §102(e) as being anticipated by Thompson et al (USP 5,824,485).

Thompson et al teach a method for screening natural pathway expression libraries for an activity of interest, including enzymes, wherein the genetic material for the expression library is from a plurality of species of organisms. Encapsulation methods taught are gel microdrops, agarose and semi-solid matrices which are assumed to encompass beads. The organisms may be a mixture of known and/or

unidentified organisms, including terrestrial microorganisms, marine microorganisms and environmental samples. Extremophile microorganisms taught include thermophiles, acidophiles and halophiles. Host cells for the expression library include E. coli (a gram negative prokaryote) and Streptomyces. Chromogenic bioactive substrates are taught and assays including immunoassays and non-fluorescent analyzers are taught. Encapsulation with an indicator cell is taught. Biopanning (prescreening) is taught. See entire document, especially col. 32, lines 62-64, col. 33, lines 36-38, col. 36, line 62-col. 37, line 9, col. 37, line 55- col. 38, line 46, col. 38, lines 47-65, col. 42, lines 57-58, col. 43, lines 36-48 and col. 46, lines 14-60.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

16. Claims 1-4, 6-15, 18, 19, 23-30, 32-41, 44, 45 and 51-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Thompson et al as applied to claims 1-4, 6-10, 18, 19, 23-30, 32-36, 39-41, 44, 45 and 51-53, and in further view of Plovins et al (App. Environ. Microbiology (1994) 60 :4638-4641) and Zhang et al (FASEB J. (1991) 5:3108-3113).

Thompson et al is applied as discussed above. Thompson et al does not teach C_{12}FDG or heating steps. Zhang et al describe the development of lipophilic, fluorogenic substrates to overcome the problems observed with the "parental" FDG. Zhang et al cite problems such as the harsh conditions required for using the FDG substrate (hypotonic shock, low temperature isotonic conditions to retard the leakage of fluorescein product). They teach that addition of the lipophilic tails to FDG would increase retention of the substrate at physiologic temperatures (thereby obviating the low temperature regimen required for FDG). They also teach that the tails enable the substrate to pass through the cellular membrane without harsh permeabilization protocols.

Plovins et al assess FDG as well as C_{12}FDG as substrates in animal, bacterial and yeast cells. They teach that these fluorogenic substrates allow for screens of all of these cells. They further compare the different substrates' performance in the different cell types: They observe that FDG is a better substrate in gram-negative bacteria than C_{12}FDG because it does not require pre-permeabilization of the gram-negative bacteria.

They teach that the (LPS) lipopolysaccharide-phospholipid bilayer of gram-negative bacteria has poor permeability for lipophilic substances such as C_{12}FDG (see column 2, page 4640 and the abstract).

The ordinary artisan would have been motivated to incorporate the fluorogenic substrate C_{12}FDG in the methods of Thompson et al because of the advantages of this substrate over FDG as taught by Zhang et al and Plovins et al who demonstrate that this substrate functions well in FACS analyses. The ordinary artisan would have been further motivated to incorporate heating steps for moderate durations into the methods taught by Thompson et al for at least two reasons. The ordinary artisan would have recognized that thermophilic donor organisms' enzymes have optimal temperatures for enzyme activity that are higher than 37°C. At the time of filing, the ordinary artisan would have been familiar with one of the most famous enzymes obtained from a thermophilic prokaryote, Taq polymerase used in PCR, which requires elevated temperatures for activity. Thus, to optimize the screening procedures, the ordinary artisan would have been motivated to elevate the temperature to obtain higher enzyme activity and decrease the frequency of false negatives.

The ordinary artisan would have been further motivated to incorporate a heating step in the methods taught by Thompson et al because of the teachings of Plovins et al who teach that permeability of C_{12}FDG into gram-negative bacteria is hampered by their lipopolysaccharide-phospholipid bilayer. They teach that C_{12}FDG penetrates damaged or dead E. coli. The heating step would damage and kill varying percentages of the library hosts depending on the duration of the step. The ordinary artisan would therefore

expect heated library cells (E. coli) to "take up" C_{12}FDG as per the teachings of Plovins et al to increase the number of library host cells which have the substrate. Thus the invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

17. Claims 1-10, 18, 19, 20-30, 31-36, 39-41, 44, and 46-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Thompson et al, in view of Short (USP 6,057,103).

Thompson et al is applied as discussed above. Thompson et al do not teach Streptomyces venezuelae, a step transferring from E. coli to Streptomyces prior to encapsulation and screening or a normalization step prior to encapsulation and screening. Short teaches methods for screening for bioactivities using libraries comprising DNA obtained from a mixture of organism. Short teach using Streptomyces venezuelae as the host cell in such methods, as well as teaching cloning fragments in E. coli then transferring them to a different host for expression and screening including Streptomyces. Short also teach normalization of the genomic library prior to screening. See entire document, especially col. 5, lines 60-67, col. 6, lines 35-36, col. 8, line 34-col. 9, line 52 and col. 12, lines 41-61. At the time the invention of filing, it would have been obvious to one of ordinary skill to combine the teachings of Thompson et al and Short. One of ordinary skill in the art would have motivated to do so because the references teach closely related subject matter, high-throughput screening methods using mixtures genomic libraries obtained from diverse organisms including extremophiles for novel bioactivities employing encapsulation. Furthermore, Short

teaches that normalization is advantageous because it allows more equal representation from the different organisms used to generate the genomic library. See col. 5, lines 13-16. Short teaches that cloning in E. coli is efficient and transferring the genomic library to another organism such as Streptomyces may overcome the potential problem that E. coli may not have the appropriate genetic background to express the bioactive compounds of interest in their active form.

Conclusion

Claims 1-53 are rejected. Claims 16, 17, 42 and 43 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

February 10, 2002

REMY YUCEL, PH.D
PRIMARY EXAMINER